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## Myotonia dystrophica :bits relationship to diabetes mellitus

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MYOTONIA DYSTROPHICA: ITS  
RELATIONSHIP TO DIABETES MELLITUS

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Myotonia dystrophica (Steinert's disease, myotonia atrophica) was first described as such, independently, by Steinert and by Batten and Gibb in 1909. Batten and Gibb discussed 15 of 29 recorded cases, as well as the five they reported, but did not ascribe the disease to heredity. (In only one instance did they report a parent with myotonia and a child with myotonic dystrophy. All other patients, in Batten and Gibb's own cases, were in the same generation.) They described the pattern of dystrophy but considered the disease much commoner in males. (1)

Thirty years later Ravin and Waring discussed the hereditary aspects of myotonia dystrophica. They decided that the disease was transmitted as an autosomal dominant, with progressive inheritance and anticipation, on the basis of the pedigrees studied. (See addenda I and II.) The dominant inheritance was not considered sex-linked since both males and females were affected and presumably the gene was passed through either sex to the offspring. (2)

In 1961 in London MacDermot reported myotonic

dystrophy through three generations--grandparent, parent, child. (3)

Ravin and his associates continued to study the above five families--13 patients in all. (4) They described the clinical features as (in addition to a family history):

- 1) Myotonia--an involuntary sustained contraction of muscles interpreted by the patient as an inability to relax. (5)
- 2) Typical pattern of dystrophy involving:
  - a) obicularis oculi and oris muscles
  - b) temporal muscles
  - c) pharyngeal muscles
  - d) masseter muscles
  - e) sternocleidomastoid muscles
  - f) forearm muscles
  - g) quadriceps muscles
  - h) dorsiflexor muscles of foot.

This pattern of dystrophy produces:

- a) nasal, easily fatiguing voice
- b) poor enunciation
- c) swan neck
- d) inability to grasp or hold

- e) slapping and/or waddling gait.
- 3) Cataracts--12 of the 13 patients studied had cataracts. These small, regular opacities with blue, blue-green and/or yellow iridescent particles were located in the posterior capsular area.
- 4) Testicular atrophy was present in three of the eight male patients.
- 5) Cholesterol and sugar tolerances were normal. The basal metabolic rate was low in all.
- 6) Mental defects depended on the family involved.
- 7) In the cardiovascular system, hypotension, bradycardia and peripheral vasomotor disturbances were often present. Of the eight patients on whom electrocardiograms were performed, two electrocardiograms were normal and six were abnormal. (4)

#### Association with Diabetes Mellitus

While Ravin and Rymer, in their studies of the five families involved, stated that the sugar tolerances were normal, (6) further studies in 1954 by Stanbury indicated

that diabetes mellitus may also be inherited by a person with myotonia dystrophica. Genetic data were not given for this woman. She, however, had myxedema at age 15, unstable diabetes at age 33, and myotonia dystrophica at age 36. She died suddenly at age 36. At necropsy no specific cause for death could be found. (7)

Jacobson performed carbohydrate metabolism studies on eight unrelated myotonic dystrophy patients in 1955. Five were given glucose tolerance tests. Two had frank diabetes, one had a diabetic glucose tolerance curve, and two had normal glucose tolerance curves. Of the two with frank diabetes, one had a family history for diabetes. (8)

In 1961 Becker and others reported three cases of myotonia dystrophica--a mother and two of her eight children. The mother also had diabetes mellitus but her two dystrophic children did not have abnormal glucose tolerance curves. Her other six children were said to be normal. (9)

In June of that year an atypical case of myotonic dystrophy was reported by Lakin. In this woman, there was progressive ocular myopathy, ovarian insufficiency



and diabetes mellitus. No genetic history was given except that two siblings did not show evidence of myotonia dystrophica. (10)

In 1962 Simon reported on 38 unrelated patients with myotonia dystrophica at the National Institutes of Health. Eleven of the 38 had diabetes, nine being controlled by diet alone. Unfortunately no data were given as to the family history for diabetes though the genetic history for myotonia dystrophica was given. (11)

In none of these reports have the family histories for diabetes mellitus and myotonic dystrophy been fully investigated. Thus it seems advisable to investigate families for the presence of both these diseases, historically and empirically.

#### Purpose

The purpose of this thesis is: To ascertain the predominance of and manifestations of myotonia dystrophica and diabetes mellitus in families having myotonia dystrophica and to ascertain, if possible, whether diabetes mellitus is inherited separately or is part of the dystrophic process.

### Characteristics

The characteristics of myotonia dystrophica are stated to be:

- 1) myotonia
- 2) muscular wasting of characteristic pattern
- 3) cataracts
- 4) testicular atrophy
- 5) family history of cataracts and myotonia dystrophica
- 6) frontal baldness
- 7) varied endocrine diseases or abnormalities
- 8) mental defect or deficiency
- 9) psychiatric disorders
- 10) nonspecific cardiac difficulties

The existence of the first five have not been called into question by investigators but the last five have been questioned.

### Myotonia

Myotonia itself was studied in the Bar Harbor strain of dystrophic mice by McIntyre and others in 1959 and on the basis of electromyographic data they decided that the muscular dystrophy was myotonic in type. (12) In

humans, Ravin and Waring in 1940 decided that myotonia was a state of continued contraction, interpreted by the patient as an inability to relax. (5)

Ravin continued his studies on myotonic muscle and studied the similarities and differences between it and a group of representative contractures and decided that the myotonic contraction was independent of associated voluntary contraction, and thus that myotonic and denervated muscle were similar. However, he cited Brown who stated that, in goats, the myotonia persists after curarization and denervation. Ravin decided that there was both a contraction and a contracture, but mainly a contraction in myotonic muscle. (13)

#### Necropsy Findings

In 1947, Black and Ravin reported on five necropsied cases of myotonia dystrophica. They examined the following structures and found:

Pituitary--Four examined:

- 1) Two anterior lobes, normal
- 2) Two anterior lobes, atrophic

Relative increase of basophilic cells.

Adrenal--Five examined:

- 1) Some cortical atrophy, especially the zona fasciculata in four; island groupings of lipoid material.
- 2) One normal, except for cortical adenoma.

Thyroid--Four examined:

Less than normally active, four.

Brain and spinal cord--Three examined:

- 1) Deficiency in anterior horn cells
- 2) Segmental differences in number of cells.

Peripheral nerves--Deficient in number of myelinated nerve fibers.

Testes--Three examined:

Atrophic in three. (14)

At necropsy on two brothers, ages 43 and 44, with myotonic dystrophy were found the following:

Testes--Two examined:

Atrophy with hyalinization of seminiferous tubules, two.

With a third necropsy (female) the following was found:

Thyroid--Three examined:

Colloid goiters, three.

Thymus--Three examined:

Persistent with fatty infiltration, three.

Obesity--Three examined:

Generalized, three.

Adrenal--Three examined:

Soft, with partly fibrotic hyperemic medulla,  
three. Irregularly degenerative, especially  
zonas fasciculata and glomerulosa, without  
lipoid deposits.

Pituitary--Three examined:

Crooke's changes of the basophils

Decrease of eosinophils and an increase  
of basophils at edge of posterior lobe

Basophilic infiltration of posterior lobe  
with atrophy

Basophilism of anterior pituitary

Colloid stasis and cysts in Rathke's cleft. (19)

At necropsy, the ciliary body was atrophied as  
reported by Vog. (18)

And at yet another necropsy (male) there was fatty

infiltration, diffuse fibrosis and hypertrophied muscle with a total weight of 340 grams in a grossly soft and flabby heart. (44)

#### Muscular Wasting

The muscular wasting has been described often and is of the specific pattern as stated above. MacDermot in 1961 described the histology of the neuromuscular junction stating that there were rows of centrally placed nuclei in otherwise intact muscle fibers. Using methylene blue, abnormalities of innervation pattern secondary to degeneration, and hypertrophy of muscle fibers were seen. She suggested that there was also a neuronal defect. (3)

#### Cataracts

Cataracts in dystrophica myotonica have been investigated extensively. In 1924 Adie had collected data on over one hundred cases of cataracts in dystrophics and their relatives. They occurred as outlined below:

Cataracts and dystrophy	66
Cataracts in dystrophic generation only	17
Cataracts in parents, aunts and cousins of dystrophics	18

Cataracts in grandparents of dystrophic  
patients

5

Cataracts in great-grandparents of a  
dystrophic patient

1

In these families the only evidence of myotonic dystrophy was the presence of cataracts except for the dystrophic patient. Adie wanted his colleagues to include myotonic dystrophy in the differential diagnosis when seeing patients with cataracts. (15)

Meyer in 1955 considered, in general, the medical significance of lenticular opacities before the age of 50 and concluded that there was cellular death (due mainly to an inability to eliminate acid metabolites or to an increase in proteolytic enzymes) and that the aftermath of this cellular death produced cataracts. (16)

In 1960 Gordin and others stated that in the dystrophics, 97.9 per cent had cataracts during the disease course, and that cataracts were the commonest and earliest of the signs of myotonic dystrophy. They did not give the percentage found in the relatives. (17)

In 1961 Vos in the Netherlands considered his cases

of myotonic dystrophy-21 females and 18 males, all of whom had cataracts. He stated that hypotension is present within the eye of the dystrophic patient with cataracts. (18)

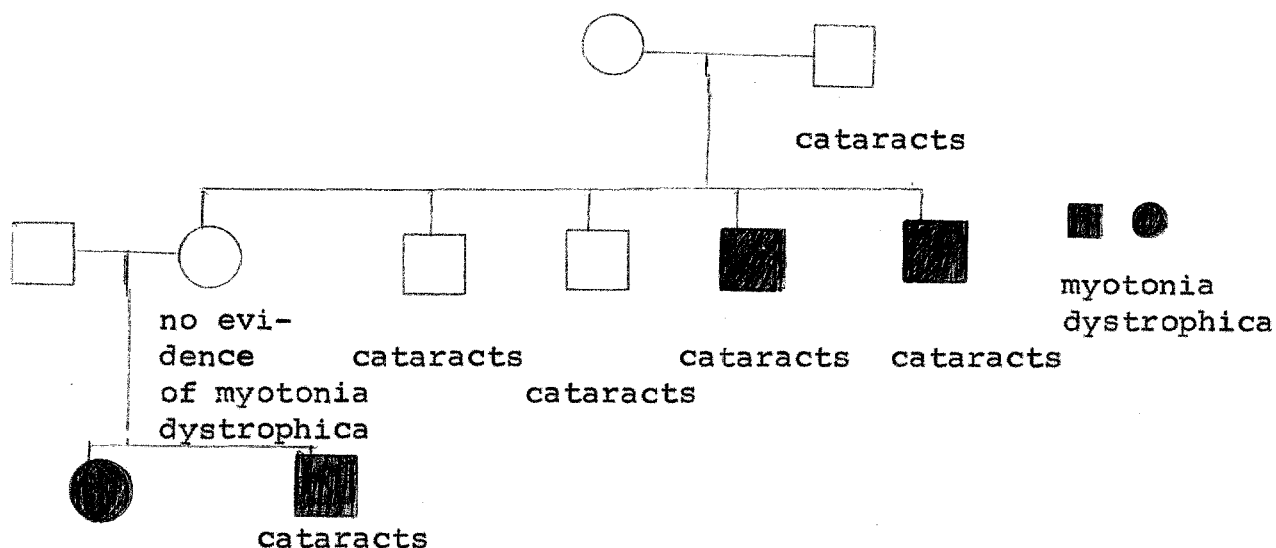
#### Testicular Atrophy

Testicular atrophy was found in many of the patients with myotonic dystrophy. On biopsy seminiferous tubular degeneration was present in two brothers, ages 43 and 44. They had hypo-excretion of urinary 17-ketosteroids and were also oligophrenic. (19) Holland and Hill stated that there was gonadal dysfunction in four of the six cases in one family they studied. (20) Clarke, in 1956, studied two cases and found atrophy of the testicular tubules but normal interstitial cells. He also found an increase in androgen and ICSH excretion, a decrease in 17-ketosteroid excretion but a normal amount of FSH excretion. (21) Marshall in 1959 studied 11 cases of dystrophy of the myotonic type. Four of the five testicular biopsies performed demonstrated irregular tubular degeneration. (22) Drucker in 1961 stated that seven of the nine patients he studied had apparent testicular atrophy. (23)

#### Family History



A family history of myotonia dystrophica and cataracts has often been found. Kings County Hospital (1960) reported one case with a pedigree as follows:



Zeigler in 1960 reported five cases, three having a family history of either cataracts or myotonia dystrophica. In another the mother was in a mental institution. (25) In only one instance in the literature, however, was genetic data given which covered three generations or more by means of examination. (3) Leach in 1962 reported a case of generalized muscular disease presenting as pharyngeal dysphagia--a 22-year-old woman with myotonic dystrophy and thyrotoxicosis. A brother had myotonic dystrophy but the father had cataracts only. (26) Another case

in 1962 presented as dysphagia, although the disease was well advanced. In this case the mother's mother had cataracts and the father had cataracts while the son had myotonia. (27)

#### Baldness

Frontal baldness has been noted often but Maas in 1937 did not consider baldness of importance in the diagnosis of myotonia. (28) However, Slatt in 1961 found premature baldness in 15 of 17 cases he reviewed. (29)

#### Endocrine Abnormalities

Reports have been circulated of an association of myotonic dystrophy with various endocrine abnormalities as well as developmental anomalies. These reports include the following:

- 1) Strabismus was reported in the Kings County case, as well as cholelithiasis. (24)
- 2) Caughey reported nine cases with gonadal atrophy with increased FSH, normal electrolytes and carbohydrate function of the adrenal cortex, low 17-ketosteroid excretion and normal parathyroid function. He believed the primary glandular defect to be atrophy of the androgenic cells of

the testes and adrenal cortex. (30)

3) Adams-Stokes syndrome, Litchfield, 1953. (31)

4) Adenocarcinoma of the thyroid, supernumerary digits and benign adenomas of the breast in one of two patients studied by Stanbury in 1954. Thyroidectomies were done at 15, 17, 21 and 24 and adenomas of the breast removed at 15 and 16 with a bilateral mastectomy at 17. One child of this patient had super-numerary digits and a high palate. A brother of the patient had myotonic dystrophy. (7)

5) Thyroid adenomas were reported by Jacobson in 1955 in two of eight patients studied. (8)

6) Nodular goiter and diabetes mellitus was reported by Marshall in 1959. (22)

7) Syndactyly, abnormal electroencephalograms and abnormal electrocardiograms were reported by Pachomov and Caughey in 1960 on six patients studied, three from one family. (32)

8) Gordin in 1960 reported an increase in creatine and a decrease in creatinine in the urine along with an increase in creatinine in the plasma but

normal plasma creatine. (17)

- 9) DiChiro and Caughey in 1960 reported skull changes. Of the 18 cases studied, the eight with proved hypogonadism had the most marked changes. Three of these 18 were acromegalics and two were completely normal. The others had changes ranging between these two extremes. They (the authors) suggested that these changes were brought about by unrestrained growth hormone released as a result of gonadal failure. (33)
- 10) Infertility and tuberculosis were reported in one family by Becker and others in 1961. (9)
- 11) Osteoporosis, fractures, decreased vibratory and pain sensation, cold intolerance and paranoia were found in a person with atypical myotonia (i.e., no myotonia, just the above and typical dystrophy). (Lakin, 1961). (10)
- 12) Hypersomnia was reported for two patients with myotonic dystrophy. (Phemister and Small, 1961) (34)
- 13) In a relative of one of the patients with hypersomnia there was coarctation of the aorta. This relative also had myotonic dystrophy. (34)

- 14) Cardiac arrest with subsequent recovery has been reported by Sciarra and Steer in 1961. They were discussing uterine contractions in a patient with myotonic dystrophy. They described slow contractility without great force and relaxation. Atrial fibrillation had occurred and upon attempted conversion with quinidine the two cardiac arrests took place. The infant was normal except for bilateral clubfoot. (35)
- 15) Narcolepsy was reported in one patient by Kuhl in 1961. (36)
- 16) Thyroid adenomas, decreased adrenal 17-ketosteroids, low 17-hydroxycorticoids and decreased 17-ketogenic steroids were reported by Drucker in 1961. (23)
- 17) Case 517 of the American Practitioner in 1962 reported an increase in FSH level, in one patient. (37)
- 18) Thyrotoxicosis with myotonic dystrophy was reported by Leach in 1962. (26)
- 19) Decreased urinary amino acid excretion, especially tyrosine. (28)

#### Mental Defect or Deficiency

Mental defect has been reported often:

Batten reported a child of a dystrophic with mental defect. (1) Benda, in 1947, reported on sibs with myotonic dystrophy and mental defect but he gives little of the family history of those without myotonia or mental defect. (19)

Zeigler in 1960 reported one of five cases of myotonia dystrophica with mental deficiency. (25)

Slatt of Toronto in 1961 states that the intelligence quotient is diminished but that the constant temperament is one of inappropriate cheerfulness, mild grandiosity and relative lack of drive. (29)

And in 10 cases, three persons with low intelligence quotients were found, one in each family. In two cases the family history was positive for myotonic dystrophy. (3)

Gibson in 1961 reported on a family, the proband being a 43-year-old woman with myotonic dystrophy, mentally retarded from birth. Her father had cataracts and two cousins of his had severe dystrophy, one also being mentally deficient. Two of the paternal sibs had physical disability of unknown type. The patient's five sibs were normal but a cousin probably had myotonic dystrophy and mental defect. This cousin and his two sibs died following a series of "heart attacks". (39)

### Cardiovascular Findings

DeWind in 1950 reported on six cases of myotonic dystrophy with cardiovascular abnormalities. In three cases, by radiography, the heart was oversized, in one case normal, in one case undersized and in one case not known. There were low P waves on two electrocardiograms, prolonged QT in three, and the electrocardiographic findings were not given in two of the cases. DeWind reviewed the literature on cardiac abnormalities and abstracted 98 cases of myotonic dystrophy with electrocardiographic findings. This total included the work of 53 authors and the cases of DeWind. Sixty-one of those electrocardiograms were definitely abnormal, with a total of 110 abnormalities noted. A table of the abnormalities follows:

	Number	Percentage
Low P	18	30
Long PR (over .20 sec.)	42	69
Long QRS (over .10 sec.)	15	25
Other:		
Elevated ST	7	12
Auricular arrhythmia	4	7

Low T waves	6	10
Hypertrophy pattern	1	2
Complete AV block	3	5
Low voltage QRS	4	7
Extrasystole	4	7
Coronary changes	2	3
Prolonged QT without prolonged QRS	4	7

Of twenty-two people with abnormal x-rays of the heart, one-half had abnormal electrocardiograms. Of the 98 cases "...it was observed that in a total of 67 patients under 45 years of age there were 38 (57 per cent) whose cardiograms showed abnormalities, and in 16 patients over 45 there were 10 (62 per cent) with abnormal electrocardiograms." (40)

In 1951 Spillane reported on 16 cases. He found the pulse "small" in six of the 16 and slow (50/minute) in two of the 16. The blood pressure was elevated in one of the 16 but was between 100-110 systolic in seven of the 16. (41) Also in 1951 Fisch reported on five cases with auricular flutter in one; left bundle branch block in one; prolonged PR interval in two and a normal electrocardiogram in the fifth. The authors considered



the etiology as undetermined. (42)

Changes of the heart and cardiovascular system are of many types but come on as a late manifestation of the disease. In 1953 Shearn reported on intermittent bundle branch block in eight patients, seven with known heart disease and one with moderately severe generalized arteriosclerosis. Since these patients subsequently had permanent bundle branch block it was considered that intermittent bundle branch block was a transition stage. The authors thought that there was pathologic alteration of the heart tissue in and around the conducting system. (43)

In 1953 Litchfield reported on a case of atrioventricular dissociation. The patient was first seen in 1941 because of short periods of unconsciousness. She had further attacks over the next nine years. In 1950 an electrocardiogram demonstrated "latent heart block" with a PR interval of .28 seconds and left bundle branch block with Adams-Stokes attacks. In 1952 she was diagnosed as having myotonic dystrophy. At that time she was re-examined electrocardiographically, with reports varying from sinus bradycardia to complete atrioventricular dissociation. She died in a syncopal

attack after she had stopped taking ephedrine. (31)

In 1954 Fisch and Evans reported on an autopsied case of myotonic dystrophy, the patient having died while walking with his son. The patient had had atrial flutter clinically and an incomplete block by electrocardiogram. (44)

In 1961 Soffer reported on a male of 44 who had a PR interval of .24 seconds. He considered this to be due to fibrous replacement of the heart muscle. (45)

Walsh, et al, in August 1963 reported on the cardiac findings in 73 patients with muscular dystrophy- 27 of them with myotonic dystrophy. Only nine of the 27 had normal electrocardiograms. (47)

#### Age of Onset

Clinically it has been said that symptoms and signs are generally observed in the twenties and thirties but first signs and symptoms have been observed from age nine months to age 70. (18, 48)

Vanier in London in 1960 reported six cases in childhood with electromyographic proof of myotonia. The youngest was nine months old. The similarities between the children were:

- 1) All were limp and floppy as a baby.
- 2) All had late motor and speech development.
- 3) All had brisk deep tendon reflexes, especially the knee jerk.
- 4) All had sucking difficulty.
- 5) All had immobile facies.

In Case 6, the nine-month-old girl, a brother was severely affected with cataracts and myotonic dystrophy. The mother was minimally affected with myotonic dystrophy. The maternal grandfather's sister had cataracts. With this strong family history it is not likely the nine-month-old child had myotonia congenita rather than myotonic dystrophy.

Case 5 was that of a 46-month-old male in whom myotonia was first noted at age three. His mother had myotonic dystrophy. A brother was severely affected with myotonic dystrophy and a half-sib had myotonia. Again, it is not likely that the child had myotonia congenita unless one assumes that myotonia congenita and myotonia dystrophica are but different manifestations of the same gene, as has been postulated.

In Case 4, the mother had myotonic dystrophy, a

sister was normal and the boy of 10 had myotonic dystrophy and mental deficiency. At age 6½ his intelligence quotient was between 80-90 on the Stanford-Binet test; at age 10 years, 5 months, his score was 70.

Cases 2 and 3 were sibs and their mother also had myotonic dystrophy. One of the sibs, age eight, was also mentally deficient.

Case 1 was a 13-year-old girl (breech delivery) with bilateral talipes, myotonic dystrophy and ineducable. Her mother had myotonic dystrophy; two older brothers were mentally deficient and also had foot deformities of some type. One sib was normal. (48)

#### Chronologic Appearance of Signs and Symptoms

The age at which the various signs appear is not known with accuracy. The Kings County case gave this chronologic appearance:

Age 14--Myotonic dystrophy

Age 27--Alopecia, vertex

Age 37--Alopecia, frontal

Age 39--Cataracts

Age 40--States that he was not impotent, although his testes were considered small. (24)

The American Practitioner gave this chronologic order:

Age 22--Partially bald, difficulty with grasp.

Age 35--Weakness

Age 40--Increasing weakness, ptosis and atrophy.

Age 43--Tubular sclerosis. Cortisone tried  
with success.

Age 53--Bedfast. Thrombophlebitis and gastric  
ulcer. (37)

#### Reproduction

It has been argued that this gene extinguishes itself for three related reasons: Infertility, sterility and such early onset that no mating is possible. Maas studied eight families with myotonia dystrophica and stated that the disease may be transmitted by persons without stigmata. He studied 215 persons in 60 sibships in those eight families. Of these, 88 persons had myotonia dystrophica with 97 living children:

	Number without children	Number with children	Total number of pregnancies	Total number of living children
Males				
23 and over	29	18	88	58
Females				
23 and over	<u>24</u>	<u>17</u>	<u>74</u>	<u>39</u>
Totals	53	35	162	97 (28)

This percentage barely reproduces the dystrophic patient.

However, families have not been studied for a sufficient duration to prove extinguishment of the gene for the above reasons.

#### Treatment Tried

Myotonia can be aided slightly by administration of quinine; however, patients seldom complain about the myotonia, and the toxic level of quinine may be required to reduce the myotonia. The progression of the dystrophy has not been aided by any therapy yet tried. Waring, Ravin, and Walker in 1940 stated that anterior pituitary extract helped one case of three and suggested aminoacetic acid, epinephrine and Vitamin E with pilocarpine. (4) Ravin in 1940 did experimental work on myotonia. He found that potassium, on oral administration (cited, 13) and a sugar solution increased myotonia. Other effects are summarized (numbers refer to number of patients on whom tried/number aided):

<u>No effect</u>	<u>Decrease myotonia</u>
ephedrine (1)	epinephrine (6/6)
prostigmine (4)	quinine (2/2)
	quinidine
pilocarpine (1)	Sulfate (2/2)

acetylcholine (1)	calcium gluconate (3)
Mecholyl (1)	(effect less marked)
atropine (1)	insulin (1/1)
benzidrine (1)	(tested three times; the more
ergotamine (1)	hypoglycemic, the less the
	myotonia)
scopalamine (2)	alcohol (1) (no effect but
caffeine (1)	probable misjudgment of
	capacity since previous
	experiments show decrease) (49)

Glaser reported three cases treated with cortisone with no improvement. (50)

Barris and Strassman in 1953 gave six patients cortisone acetate and after seven to eight days of therapy a decrease in time required to relax muscles occurred. Within 72 hours after cessation of therapy the myotonia returned to its pre-test levels. (51)

Martin and Pattee in 1954 gave cortisone to two patients with myotonic dystrophy. In both patients cortisone produced improvement but there was a remission within six weeks in one. (52)

In another article the effects of other drugs on myotonia are given:

#### Decrease Myotonia

Glucocorticoids

Glutamic acid

Sodium lactate

Insulin and glucose (not very effective)

Glucose only

Insulin and lactate (32)

Leyburn tried an ion-exchange resin and with a decrease in the potassium concentration in the serum produced a decrease in the myotonia for so long as the treatment persisted. He used a sodium polystyrene sulfonate and produced a shortening of the myotonia but no abolishment of myotonia, slight objective improvement in two of the eight patients but subjective improvement in none. (May, 1960) (53)

In a case of myotonia congenita and one of paramyotonia Norris in April, 1962, studied myotonic depolarization by intracellular recording techniques. He found a nearly linear depolarization which was apt to terminate in a normal depolarization spike potential. This was usually followed by another slow depolarization. He thought that procaine amide seemed to abolish the second depolarization or at least reduce the number of fibers showing it. (54)

Paterson in May, 1962, stated that methonium drugs



should not be given since spasm of muscle occurs with their use. (55)

Treatment for accompanying endocrine diseases or the cardiac abnormalities is symptomatic and compensatory.

#### Reaction to Anesthesia

In 1960 Kaufman in London reported on 79 cases of myotonia--eight of them being myotonia congenita and 71 being dystrophica myotonia. He commented on the reaction to anesthesia of these patients. Since only 25 had full data available on the operations performed he discussed only those. He separated them into four groups:

I--uneventful	
a) local anesthesia	4
b) general anesthesia	11
II--myotonic attack	1
III--respiratory complications	5

The operations were:

Cataracts  
Hernia  
Urethral bar resection  
(auricular flutter developed)  
Dental extraction

All had morphine pre-operatively.

IV--mortality	4
---------------	---

All these patients were markedly debilitated. Operations were:

Polycystic kidneys

(BUN 300 mgm. %)

Caesarian section

Gastrectomy

Cholecystectomy

(56)

#### Chromosomal sex

With the great emphasis on hereditary diseases associated with or caused by chromosomal abnormalities, and considering that the physical appearance of those males with myotonia dystrophica is not unlike that found in Klinefelter's syndrome--the chromosomal sex of the patient has been checked and compared with phenotypic sex. In the patient reported by Ledwith, et al, in January of 1961 the sex chromatin was negative in a phenotypic male. (57) Lakin reported the sex chromatin in a case of an atypical dystrophic phenotypic female as positive in June, 1961. (10) Drucker, in his study of 17 patients, nine of whom were males, reported one chromatin positive smear from a phenotypic male. He does not state how many smears were performed or on how many patients. (December, 1961) (23)

#### Psychiatric Evaluation

Billings and Ravin reported on a study of 11 patients

in five family trees. Eight were males, three females and of these nine had myotonic dystrophy. The evidences they demonstrated were apathy, depression and enfeeblement on first appearance. However, they co-operated easily. Urge and drive were not diminished but ability to carry out urge and drive were. The authors stated it was not possible to corroborate the findings that the more the muscular dystrophy, the more the intellectual impairment or retardation. Because of the insidiousness of the disease there is time for the patient to adapt. (58)

#### Inheritance of Diabetes Mellitus

Diabetes mellitus, a disorder of carbohydrate metabolism, was known to have a family incidence as early as the seventh century in India, (59) but it was not until the 1930's that Pincus and White demonstrated its hereditary nature. (60) The pattern of inheritance is still in doubt with most authors agreeing that diabetes is inherited as a recessive gene and is manifested only in the homozygous state (61, 62, 63), but a dominant gene with incomplete penetrance is also suggested. (64,65)

Simpson, in 1962, studied 233 families of juvenile diabetics, in order to ascertain whether juvenile diabetics

had a greater proportion of children who were diabetic than could be expected on a statistical basis, and to ascertain, if possible, the exact pattern of inheritance. The data, according to Simpson, indicated "that the predisposition for diabetes at an early age is under genetical influence which is not compatible with the single gene hypotheses of recessive, intermediate or dominant inheritance. Genetic heterogeneity between juvenile and adult diabetes is suggested and discussed. Theories of multiple genes or modifying genes for age at onset together with a single gene for the predisposition of diabetes cannot be distinguished from the data." (66)

However, Nilsson in Sweden conducted a survey in young males of military age for the purpose of elucidating the hereditary background of diabetes, especially of the juvenile type. The diabetics in Series A were matched against Series B--made up of young male relatives of diabetics and a control group. A genetic-statistical analysis was then made with the following conclusion: "The values obtained indicate, after correction for age, that about 15% of the children of diabetic parents will sooner or later develop diabetes and are well consistent

with an autosomal recessive inheritance and a gene frequency of 0.15-0.20. The similar figures when the parents are requiring and not requiring insulin argue in some degree for a uniform diabetes gene and against the assumption that mild diabetes not requiring insulin should be more common in heterozygotes.

"Here, too, a dominant inheritance with a gene frequency about 0.05 and  $P_{max}$  30% is compatible with the values found.

"As is apparent from the above comparisons, good agreement was found between the expected and observed values on the assumption of an autosomal recessive mode of inheritance and then best with an assumed gene frequency of 0.17-0.20 and a maximum penetrance of 60-70% in male homozygotes and of 80-90% in female homozygotes....

"A dominant inheritance with a gene frequency of about 25% in males and of about 30% in females could be an alternative but less probable interpretation of the observed values." (67, pages 28-29)

"Under certain conditions heterozygotes may also develop this disease, and this may then help to explain

a certain overmorbidity among groups in which the frequency of diabetes is definitely higher than the 4% expected with a gene frequency of 0.2 and manifestation in homozygotes only....

"It seems probable that also other blood-sugar enhancing factors, e. g., cortisone, administered, or produced in increased amount indirectly stimulate the beta cells to an increased production of insulin, which may result in an undue stress on the insulin producing apparatus." (67, page 60)

If, then, diabetes is inherited as an autosomal recessive with a frequency of 0.15-0.2, one would expect 40,000,000 carriers in a population of 200,000,000 and about 6,400,000 diabetics (estimating 80% penetrance in the homozygote state). The population of the United States is approaching the 200 million mark and the number of diabetics is estimated at five million. Thus diabetes mellitus is a very common hereditary disorder--the possibility of being a carrier is one in five (20%) and the possibility of becoming a diabetic is about one in 35 (2.5%)

Association with Myopathy

No data are available.

See Addendum III for compilation of laboratory data from the literature.

Three families have been studied--the S family, extensively; the D family and the K family. Pedigrees are presented in Addenda IV, V, and VI.

S Family

The S family is descended from I-2 and his two wives, I-1 and I-3, none of whom are related. A short description of each member of the family will be given, with all available pertinent data on each:

I-1 The first wife of I-2, she and I-2 had four children, II-1 through II-4. Born in Czechoslovakia, she was stated to be in good health until her death by suicide at about age 25 circa 1870 in Nebraska. She was without known diseases and had no siblings.

I-2 The grandfather of the proband. He and his two sisters, his only siblings, came to the United States from Czechoslovakia. The tracing of these sisters and their progeny is being done. Born in 1852 and dying in 1925, he was stated to have heart disease, cataracts with ptosis and diabetes mellitus. His death certificate confirmed only the diabetes (diagnosed by the



finding of sugar in the urine) and gangrene of the foot. He had a total of 12 children by both of his wives.

I-3 The second wife of I-2, she was an only child, born in Czechoslovakia in 1861 and dying in 1923 after 1½ months paralysis. She was stated to have heart disease and to be weak but diabetes mellitus and cataracts with ptosis were denied. She and I-2 had eight children, II-5 through II-12.

II-1 The only information on this man was from the proband who stated that II-1 died in an accident on a ranch at about age 19 circa 1890. He was single. Nothing is known about his state of health.

II-2 II-2 and II-4 were fraternal twins. II-2 was born in 1881 and died in 1950. She was the second wife of her husband, bearing him four sons, III-1 through III-4. She was stated by the proband to have no diseases and to have good eyesight. However, the death certificate stated that death was due to myocardial

insufficiency of three weeks duration, due to chronic myocarditis for five years.

II-3 This man was born in 1885 and died in 1947.

He was married to a sister of the husband of II-5. He was stated by the proband to have no heart disease, no diabetes, and no muscular wasting. By death certificate, he died in cardiac failure of two hours duration, secondary to a ruptured appendix and mild peritonitis. He had two sons, III-5 and III-6.

II-4 This man was the fraternal twin of II-2, his sister. He never married, and was considered by his kin to be mentally retarded. He died in a mental hospital, whose records showed him to be mentally deficient, to have a psychosis and also to have chronic myocarditis. He was also stated to have a congenital dislocation of the hip. He was born in 1881 and died in 1946.

II-5 This woman was stated to have had ptosis, a cataract, a questionable heart attack and a distended stomach for two years before death. Born in 1898 and dying in 1944, she bore her

husband one daughter, III-7. Her death certificate stated that she died of acute cardiac dilatation due to chronic myotonia of two years, due to inheritance in the family.

II-6 This girl died of typhoid fever at age two circa 1894. Nothing more is known.

II-7 This man and II-9 are the only children of I-2 still alive. Born in 1901, II-7 is married and has two children. He has myotonia dystrophica, has had cataracts, does have ptosis and does have heart disease. He has had weakness for 15 years, difficulty walking for 10 years, and ptosis for five years. He has pectus excavatum, high arched palate, frontal and occipital baldness and testicular atrophy.

II-8 Born in 1890 and dying in 1962, he had four children, III-10 through III-13. II-8 was stated to have heart disease and lip cancer but no muscular weakness or wasting, cataracts or diabetes. He did wear glasses. By death certificate he was stated to have an acute coronary occlusion with marked cardiac hypertrophy with a very loud mitral murmur. His wife has

diabetes mellitus.

II-9 Born in 1888 and still living, she was married, had one miscarriage but no children. She is stated to wear glasses but otherwise to be very alert.

II-10 The mother of the proband, she was born in 1889 and was stated to have had cataracts with ptosis, diabetes mellitus, a goiter operation (at Mayo's), and a cataract extraction. A description stated that she had "piano legs, slender, pointed fingers, very thin from hands to elbows, and from feet to knees" but weakness was denied. By death certificate she was stated to have died with a pulmonary embolus, due to coronary artery disease. She and her husband had four children: III-14, the proband; III-15, his brother, and III-16, his sister. The fourth child was a stillborn child (girl).

II-11 Born in 1895 and dying in 1962, he never married. He was stated to have cataracts with ptosis and heart disease but diabetes mellitus and myotonic dystrophy were denied. By death certificate he died from a pulmonary

embolus, due to a fractured tibia, due to a fall.

II-12 Born in 1894 and dying in 1962, he was married twice, having three children, III-17 through III-19 by his first wife and III-20 by his second wife. He was stated to have heart disease and to wear glasses but not for cataracts. Diabetes and muscular dystrophy were denied. He was stated, however, to have been unable to use his hands and arms for about 10 years but these symptoms cleared. Death certificate: pulmonary embolus with a 10-year history of cardiac decompensation, acute coronary occlusion with contributory coronary sclerosis.

III-1 Born in 1901 and dying a suicide, in 1951, he married about one month before his death; his wife died, reason unknown; he then committed suicide. He was stated to be in good health.

III-2 This man was stated to have been born in 1900, to have married and to have one daughter, IV-1. He is supposedly living.

III-3 This man was born in 1908 or 1909, and became a patient at UNH in 1941 at which time he was given a diagnosis of progressive muscular

dystrophy, hereditary. He has not married and is presently a patient at the state hospital in Niobrara. The physicians there state that this man has myotonic dystrophy. In 1941 he was noted to have muscular dystrophy, some dyspnea on exertion, and atrophic testes. Lens opacities were not noted at that time.

III-4 This man was born in 1905 and is still living in Washington state. He is divorced but had three children by his marriage, IV-2 through IV-4. Except for anemia he has no other known diseases.

III-5 This man is about 47, is married, has no children and had two ribs removed because of "decay."

III-6 This 50-year-old Army veteran is married and has four children, IV-5 through IV-8. No diseases are known.

III-7 This 34-year-old female is married and has three children, IV-9 through IV-11. She is stated to be over six feet tall with a mannish build.

III-8 This daughter of a known myotonic patient is

24, is married and has one daughter, IV-12.

No attempt has been made to contact her, since her mother so requested.

III-9 The brother of III-8, he is 31, a Korean War Army veteran and single. He has been examined here and exhibits a pectus excavatum, a high arched palate, and a questionable beginning weakness of his hands. An electrocardiogram was within normal limits.

III-10 This married male born in 1914 has three sons, IV-13, IV-14 and IV-15. He has no known diseases.

III-11 This 37-year-old female with myotonic dystrophy was born in 1926, is married and has one son, IV-16. She has been examined and has both clinical and electromyographic evidence of myotonia dystrophica. Skull x-rays were normal. She has had four known abortions, and has had cysts on both ovaries. Other laboratory data will be presented in the tables.

III-12 Born in 1918, he has myotonic dystrophy. He is married and has one living child, IV-17. Two still-births were reported. One kidney was

removed in the Army (World War II) for infection.

III-13 A 51-year-old male born in 1912, he is married and has three children, IV-18 through IV-20. He is stated to have no diseases. His work requires much physical activity.

III-14 The proband is 55, born in 1907 and single. He has myotonic dystrophy, cataracts, heart disease and diabetes mellitus. Other data are presented in the tables.

III-15 The proband's brother was born in 1917, is married and has four children, IV-21 through IV-24. He had a normal physical examination except for a high arched palate. He has no known diseases.

III-16 The proband's sister was born in 1924, is now 38, single and mildly mentally retarded. She has myotonic dystrophy, has had a uterine tumor removed, early cataract, pectus excavatum and a high arched palate. She has been "pigeon-toed" since early childhood.

III-17 A 44-year-old male born in 1918, he is divorced and has no children. He was stated by the proband



to have no diseases. However, he has been repeatedly hospitalized for leg ulcers. At one hospital, a possible diagnosis was made of Klinefelter's syndrome. At another, testicular atrophy, slow responses, a small sella turcica by x-ray, BMR's of --9% and --23% and a normal glucose tolerance test were discovered. A photograph of him at that time demonstrated ptosis but not cataracts. On the basis of the above a diagnosis of probable myotonic dystrophy has been made. He has refused all requests for physical examination and tests.

III-18 This sister of III-17, is 40, is married and has two children, IV-25 and IV-26. She is stated to have cataracts but denies all else except an operation on her lumbar spine. She has been quite resistant to interviews or examinations.

III-19 Born in 1925, she is stated to have cataracts with ptosis. She is married and has one son, IV-27, and is stated to have had two stillborn girls. Contact has not yet been accomplished.

III-20 The half-sister of III-17, III-18 and III-19 through her father, she was born in 1931 and is married with one child, IV-28. She was stated to have had thyroid surgery and an hysterectomy for uterine fibroids.

IV-1 She is 18 and at home.

IV-2 Born in 1943, she lives in Washington state.

IV-3 Born in 1934, he is married and has four children, V-1 through V-4. He lives in Washington state.

IV-4 Born in 1933, he is married and has one child, V-5. He lives in Omaha but has not replied to questionnaires.

IV-5 and IV-6 are girls and IV-7 is a boy.

IV-8 Born in 1947, he died in 1960. A congenital interventricular septal defect was repaired in 1959 with apparent good results but 16 months later he died with severe pulmonary hypertension. Except for a foot infection once, he appeared otherwise normal.

IV-9 is a nine-year-old male; IV-10 is a 10-year-old male and IV-11 is a one-year-old female

living in Minnesota.

IV-12 is a two-year-old girl and IV-13 is a ten-year-old boy.

IV-14 An 18-year-old male, he is married and has one daughter, V-16.

IV-15 A 21-year-old male, he will soon marry.

IV-16 This six-year-old boy has a high arched palate but otherwise appears normal.

IV-17 A girl.

IV-18 About this four-year-old boy, nothing is known. Nor is there anything known about IV-19 who is 21.

IV-20 A female born in 1939, she is married and has two children, V-7 and V-8, and is stated to be without abnormalities.

IV-21 The 10-year-old nephew of the proband, he weighs 90 pounds and is stated to be strong.

IV-22 The 11-year-old nephew of the proband, he is very strong though he weighs only 74 pounds.

IV-23 The proband's 12-year-old niece, she has no known diseases.

IV-24 The proband's eight-year-old niece; she wears glasses, is tall for her age and weighs 80 pounds.

IV-25 This 14-year-old boy; IV-26, a 16-year-old girl; IV-27, a 12-year-old boy who is fat; and IV-28, a six-year-old boy, are stated to be without known diseases.

V-1 This boy was born in 1956; V-2, a boy, 1957; V-3, a boy, 1958; V-4 and V-5, girls, in 1959; V-6, a girl in 1963; V-7, a boy, in 1959; and V-8, a boy, in 1961. Nothing more is known concerning them.

#### D Family

This family is descended from I-1 and I-2.

Attempts to trace the disease to either side of the family have so far failed although II-2 states that she believes it came from her husband's side.

I-1 He was born in 1873 of Irish descent, but he lived most of his life in Kansas. He died in 1950 at 77 and was stated to be blind, probably due to cataracts, and to be bedfast with a stroke. By death certificate he was said to have congestive heart failure, with senility and avitaminosis for three years previous to his death. He and I-2 had four children, II-1 through II-4.

- I-2 I-1's wife, she is 70 and mentally dull (so her physician stated). Her great-grandfather came from England, though she was born in Kansas. She has arthritis, skin cancer, and a floating kidney, but otherwise is stated to be normal.
- II-1 A male infant born in 1913, he died at age 10 days from septicemia.
- II-2 This 38-year-old woman is married with four children, III-1 through III-4. In a report on one of her nephews, it was stated that his maternal aunt had myotonic dystrophy. Nothing else is known except that she wears glasses.
- II-3 This 45-year-old male has myotonic dystrophy in advanced stage. Cataracts are present. He has one son, III-5.
- II-4 The proband was born in 1922. She has been married twice, all four children as well as two miscarriages being products of the first marriage. She has myotonic dystrophy, has cataracts and has had an hysterectomy for menorrhagia.

- III-1 This 21-year-old male is said to be normal, is married and has one living child, IV-1, and a full-term male infant who died shortly after birth.
- III-2 This 19-year-old female is married and is stated to be free of disease.
- III-3 A 15-year-old female stated to be retarded, she lives at home.
- III-4 This is a 12-year-old girl.
- III-5 This 19-year-old son of a myotonic was in the Navy and is said to be normal. He is presently attending an electronics school.
- III-6 This is the 20-year-old son of the proband. He is said to have myotonic dystrophy, to be mentally retarded, to have had bilateral clubfeet and at age 14, his head circumference was 51 cm.
- III-7 This 17-year-old sister of III-6 is slightly mentally retarded, is oddly proportioned and very small for her age. She had a diagnosis of myotonia congenita given her. She has nasal speech. Her maturationally underdeveloped ears and her hands are said to be very small and she

is said to be underdeveloped sexually. She has a large head.

III-8 This is a 14-year-old boy whose intelligence ranges in the bright normal, verbal 120, performance 104 and full scale 114. He has a Grade II systolic murmur thought to be functional; an exaggerated lordotic curve; a nutritional anemia, and absent abdominal reflexes. He showed some emotional instability.

III-9 This 13-year-old boy weighed 6 pounds, 8 ounces at birth but was in poor condition and kept in an incubator for 43 days. He had slow development but no muscle impairment, although he does have hypernasality. His intelligence quotient at age 10 ranged from 48 to 54, and his retardation is said to be on a congenital organic basis. He has a large head with an asymmetry in skull development--an underdevelopment of the left parieto-occipital region of the calvarium.

IV-1 This three-year-old girl is said to be normal.

IV-2 This full-term male infant died shortly after birth, possibly due to a congenital heart

lesion.

K Family

This family is descended from II-6 and II-7.

Although names and some data are known concerning members from both II-6 and II-7's families, nothing that is known throws light on the inheritance of myotonic dystrophy in this family from either side.

A summary follows:

II-6 Born in 1880 in South Dakota and dying in 1953, he had cardiac failure, a myocardial infarction, coronary occlusion, arteriosclerosis and hypertension according to the death certificate. By history from III-7, he wore glasses and was going blind before his death. He was also stated to have had an eye operation in his early youth, and in photographs of him as a young man, there is a definite strabismus. He and II-7 had three children.

II-7 Born in 1888 in Wisconsin, she died a suicide by drowning.

III-5 Born in 1916, he has four children, IV-1 through IV-4. Nothing else is known except that they live in Minnesota.



III-6 Born in 1914, she married and had one miscarriage and four children, IV-5 through IV-8. She has had a bilateral salpingoophorectomy and hysterectomy for leiomyoma with menorrhagia. There is a possibility of myotonic dystrophy in this woman as evidenced by her photographs. She will be examined as soon as possible.

III-7 This man, the proband's father, was born in 1909 in South Dakota. A high school graduate, he was partly bald, had cataracts, had a high forehead, had a high arched palate, and had myotonic dystrophy and ptosis. He noticed the onset of myotonia dystrophica at age 25 with the loss of grip. He was hospitalized in 1948 with a "heart attack"; there was paroxysmal shortness of breath in 1953. In 1955 at the Mayo Clinic he was diagnosed as having myotonic dystrophy, coronary sclerosis and angina pectoris. At that time he had a right bundle branch block. An appendectomy was performed in 1956. A cystic spermatocoele was removed in July of 1963. He denied diabetes mellitus. He and his wife had three children, IV-9 through

IV-11. He died in December, 1963.

IV-1 A girl of 19, she is married.

IV-2, IV-3 and IV-4 are boys aged 18, 14 and 12.

IV-5, IV-6 and IV-7 are girls of 23, 20, and 19, and  
are all going to business college.

IV-8 is a boy of 14, living at home.

IV-9 The proband was born in 1937 and finished her  
junior year in high school. She has myotonic  
dystrophy and a high arched palate. She had  
a tonsillectomy and adenoidectomy at age nine.  
At 10 and 13, foot operations for congenital  
pes planus were performed. Myotonia was first  
noticed in the eighth grade (13-14 years). At  
age 17, her left kidney was removed for infection  
preceded by hydronephrosis (probably congenital).  
She is not married.

IV-10 She is 21, married and has two sons. She  
finished the first semester of college.  
Myotonia is denied. In 1962, she had vertigo  
with a Meniere's-like syndrome, etiology unknown.

IV-11 Born in 1947, she has finished the eighth grade.  
She received a diagnosis of myotonic dystrophy  
in 1959 at Mayo's on the basis of electromyographic

studies. At that time she had a full scale intelligence quotient (WISC) of 84. She has a high arched palate.

V-1 This is a two-year-old boy, stated to be in good health.

V-2 This is a six-month-old boy said to be in good health.

#### DISCUSSION

##### Inheritance

##### Myotonia Dystrophica

In the S family, of I-2's 12 children, two have proven myotonic dystrophy (II-5 and II-7); three have probable dystrophy (II-2, II-8 and II-10) since some of their children have proven dystrophy, and two others had possible myotonic dystrophy (II-11 and II-12). This incidence (proven and probable) of 41 per cent, approaches the expected incidence (.5 or 50 per cent) in Generation II.

Of I-2's twenty grandchildren, five have proven myotonic dystrophy and two others have probable myotonic dystrophy. The proven cases fulfill the 25 per cent expected in Generation III.

No proven or probable case of myotonic dystrophy has appeared in Generation IV or in Generation V. However, only one member of Generation IV has been examined and no member of Generation V. Very few Generation IV members are old enough to bear children. Generation V members are progeny of as yet unaffected Generation IV members.

Of Generation II's seven affected members, (proven, probable or possible), six are married and have 18 children. Of these 18 children, one would expect nine cases of myotonia dystrophica. In fact, five are proven, two are probable and two are possible dystrophics.

Of the five proven dystrophics of Generation III, two are married and each has a child. Of the two probable dystrophics, neither is now married and neither has children. Of the two possible dystrophics, each is married and has a child or children. None of these children are old enough to marry.

#### Inheritance--Diabetes Mellitus

Three cases of diabetes mellitus were discovered--all of maturity-type. I-2, by death certificate, had diabetes mellitus. The proband's mother had diabetes

controlled by diet alone. The proband has diabetes. No other cases of diabetes have been found by death certificate, history or tests.

Inheritance--D family

Myotonia dystrophica

Of I-1 and I-2's four children, two have proven myotonic dystrophy and one possibly has myotonic dystrophy (expected incidence of 50% proven). Of their nine grandchildren, two have proven myotonic dystrophy--an incidence of 22 per cent (expected--25 per cent). There is only one living member of Generation IV, born to an as-yet-unaffected member.

Diabetes Mellitus

No cases of diabetes mellitus have been found, by death certificate, history or examination.

Inheritance--K family

Myotonia Dystrophica

There are three cases of proven myotonic dystrophy in this family--in III-7 and two of his three daughters. A sister of III-7 (III-6) may have myotonic dystrophy. A further family history of myotonia dystrophica has not yet been elicited.

### Diabetes Mellitus

No cases of diabetes mellitus have been elicited, by death certificate, history or examination.

Myotonic dystrophy is inherited as an autosomal dominant gene. Diabetes mellitus is considered by most authors to be inherited as an autosomal recessive gene with expression only in the homozygous state. Thus a person could be a carrier of the gene for diabetes mellitus without having signs or symptoms (at least not detectable by present techniques). In the S family, the only family of the three with any history of diabetes, the three diabetics (mature in type), all have myotonic dystrophy as well. Five members in the S family have had sugar metabolism tested, either by fasting blood sugars or glucose tolerance tests. Also included in the table are laboratory data from the other families:

Patient	Myotonia Dystrophica	FBS mgm.%	2-hr. P.P.	<u>Glucose Tolerance Test</u>
S-III-14	yes	125	214	none performed
S-III-16	yes	68	---	none performed
S-III-17	yes (?)	117	---	104 143 120 100 79 100 109
S-III-11	yes	81	---	none performed
S-IV-16	no	73	---	none performed

K-IV-9	yes	70	---	54 115 77 63 60 55 55
K-IV-11	yes	60	---	73 137 100 NS 70 74 76
K-III-7	yes	74	---	71 147 93 NS 68 64 72
D-II-4	yes	--	---	90 114 74 76 79 78 82

Thus the glucose tolerance curves of these patients are essentially flat and not diabetic in type.

On a sum total of 47 patients reported (22, 9, 10, 34, 6, 11, 7, 8, 32, 53, 46) the results were as follows:

glucose tolerance tests:

flat	4
normal	18
reactive hypoglycemia	1
diabetic	14
abnormal	$\frac{4}{41}$

fasting blood sugars:

normal (60-100)	5
elevated	$\frac{1}{47}$

In none of the families reported in the literature were family histories for other than myotonia dystrophica (and especially were they not given for the 11 diabetics reported by Simon (11) ).

Other laboratory data on the three families:

Patient	myotonia	Ca mgm%	K meq/l	Na meq/l	Cl meq/l
S-III-14	yes	9.3	4.0	143	106
S-III-16	yes	11.6	4.6	150	103
S-III-11	yes	---	---	---	---
S-IV-16	no (?)	---	---	---	---
K-III-7	yes	9.0	3.9	133	100
K-IV-11	yes	---	---	---	---
K-IV-9	yes	9.3	---	---	---

Patient	Mg mgm%	P mgm%	serum creatinine mgm%	PBI mcg%	cholesterol mgm%
S-III-14	---	2.7	0.68	6.5	---
S-III-16	---	---	---	6.8	265
S-III-11	3.5	---	0.71	4.5	278
S-IV-16	2.3	---	0.54	4.0	200
K-III-7	2.45	---	---	---	262
K-IV-11	2.3	---	---	---	172
K-IV-9	---	2.5	---	---	---

Electromyograms were performed and were positive for myotonia on S-III-14, S-III-16 and S-III-11.

Basal metabolic rates were done on S-III-17, (--9% and --23%) and on S-III-3 (--10% and --9%).

Cholesterol on S-III-7 was 309 mgm% and on S-III-3 was 270.

Urinary steroids were performed on:

	17-ketosteroids	17-hydroxysteroids	17-ketogenic
(Normal)	7-18 mgm	7-18 mgm	7-18 mgm
S-III-16	5.9	---	---
K-IV-9	3.8	5.1	8.4
	3.5	5.2	8.6



Thus serum calcium, potassium, sodium, chloride, and magnesium levels appear normal. Phosphorous levels appear depressed (normal 3-4.5 mgm) as do serum creatinine levels (0.8-1.6 mgm%). PBI's of four patients (three with myotonia) appear to be in the normal range. Cholesterol levels are at the upper level of normal. The 17-ketosteroid and 17-hydroxy urinary steroids are depressed.

Electrocardiograms were performed with a first-degree AV block, LVH, ischemia and hypokalemia in one; atrial fibrillation, LIV block or possible LVH in another; 1st stage AV block and LVH in a third; wandering pacemaker in a fourth (not presently a myotonic patient); and two more within normal limits for a total of six.

Muscle biopsies were performed with three of the four being diagnostic for muscular dystrophy.

Expected incidence of diabetes is 0.15-0.20 (69 members--2-3 diabetics expected; 3 diabetics found). It thus appears, in a study of these families for both diabetes mellitus and myotonia dystrophica, that the presence of diabetes in these patients is a casual one.

If it is postulated that the diabetes is due to

exhaustion of the beta cells by mechanisms of the type found in acromegaly, Cushing's syndrome, hemochromatosis or other rare conditions, then is myotonia one of those rare conditions?

Acromegalics develop diabetes (25% have frank diabetes) and it is assumed that this is due to an increase in STH which unduly stresses the beta cells. In myotonics, it has been said that androgen producing cells in the testes and adrenal cortex fail and thus restraint on the production of STH is released. While this might cause diabetes, this theory does not explain the flat glucose tolerance curves obtained in the patients.

Is too much cortisone being produced--thus indirectly stimulating the beta cells? Evidence shows decreased amounts of adrenal steroid excretion products.

Is there fibrosis, as in hemochromatosis? Autopsy studies do not indicate this (though whether the patients had diabetes is not known).

#### SUMMARY

Three unrelated families with myotonia dystrophica were questioned, and some were examined for the presence of diabetes mellitus and myotonia dystrophica. No new

cases of diabetes mellitus were discovered, other than those already known. In the S family consisting of 69 members, three members with myotonia dystrophica were found to have diabetes, another ten proven or probable myotonics were discovered. Thirty-six of the 69 are not yet of the age when myotonia usually begins to exhibit itself. In the other two families, no diabetics were found.

It appears that myotonia dystrophica and diabetes mellitus are associated only casually in these families, since statistically two to three diabetics could be expected.

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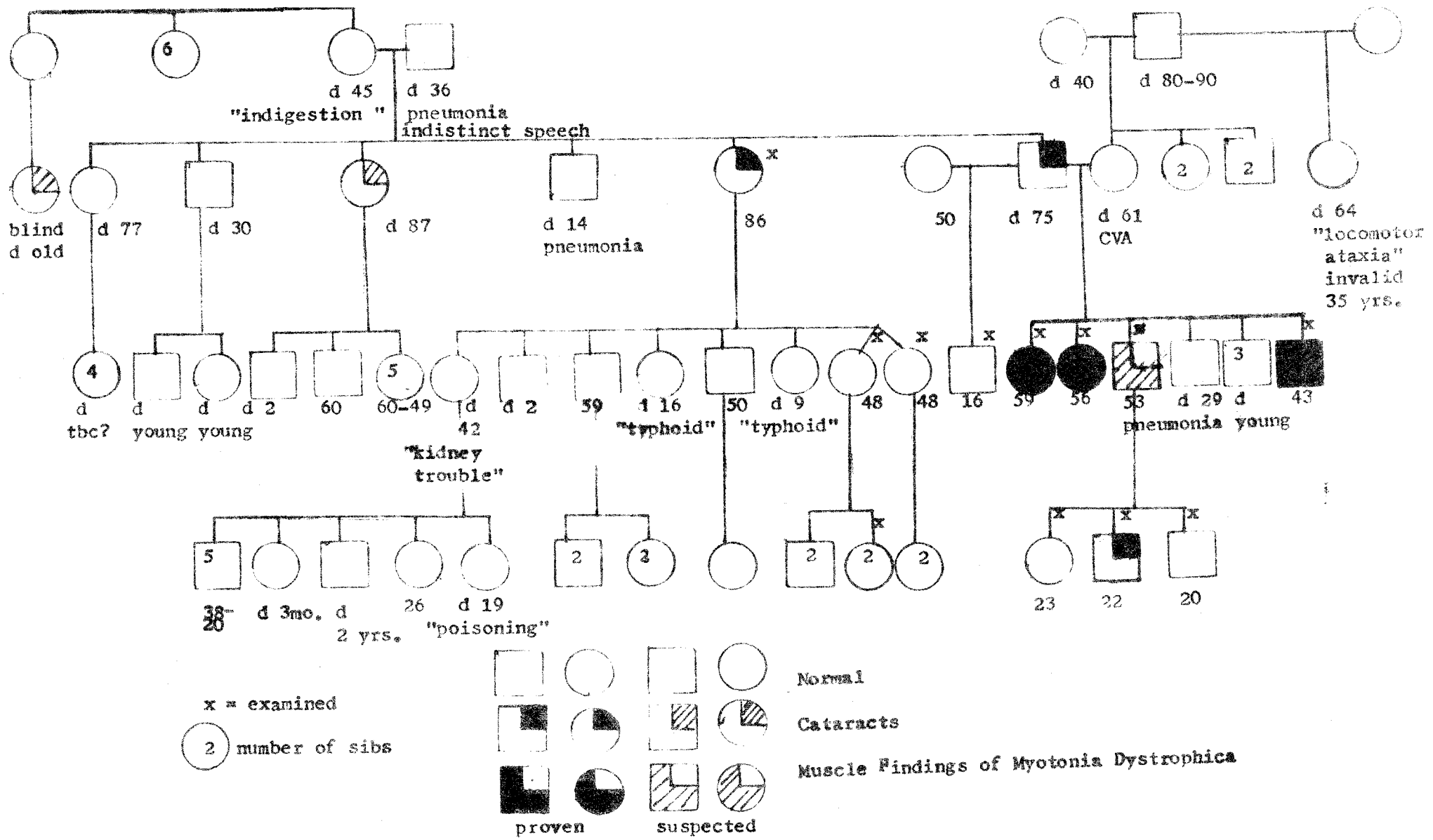


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# ADDENDUM I

## M Family Pedigree

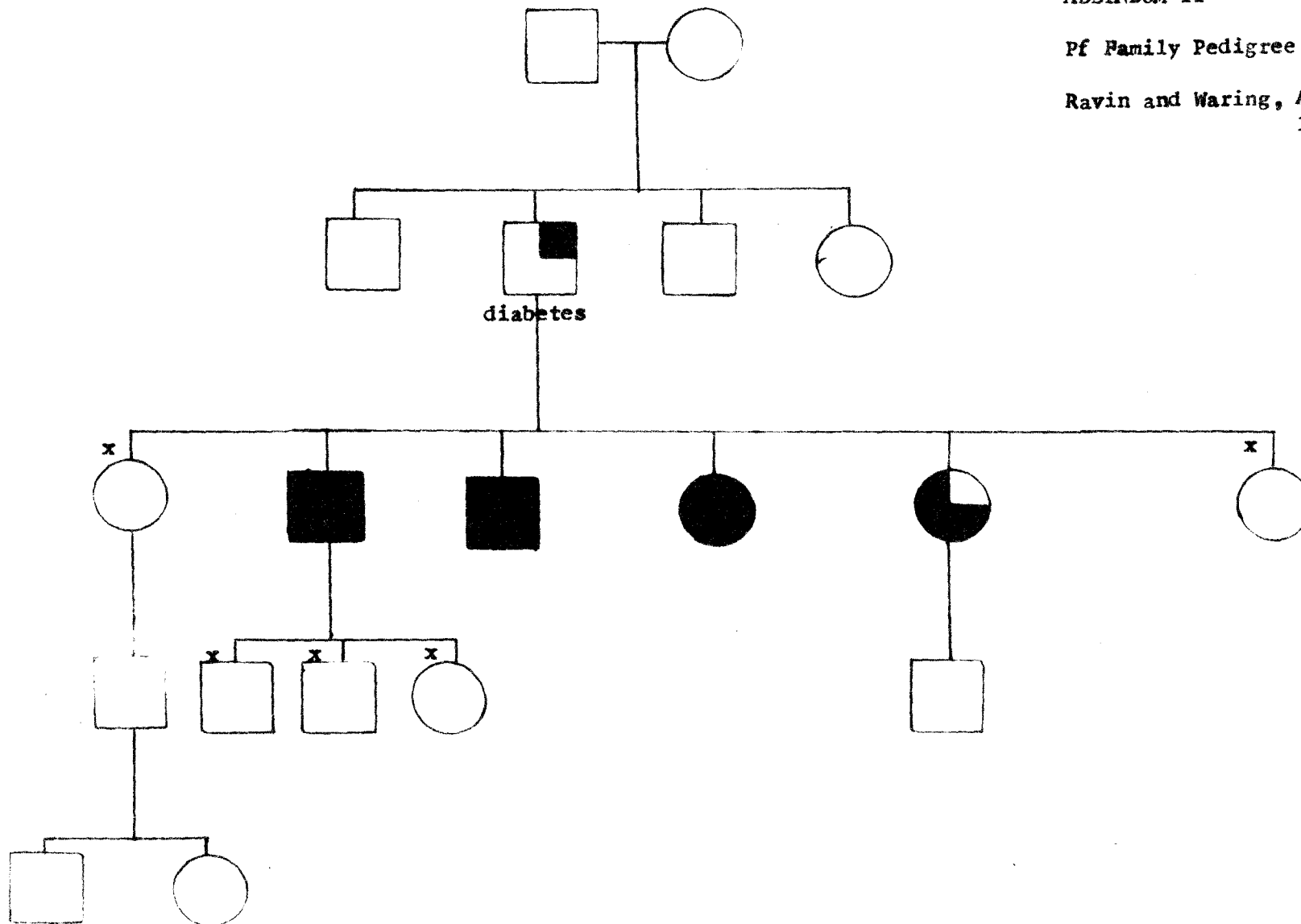
Ravin and Waring, Am. J. Med. Sci. 197:593, 598



ADDENDUM II

Pf Family Pedigree

Ravin and Waring, Am. J. Med. Sci.  
197:593



Legend same as for M Family

# LABORATORY DATA FROM LITERATURE

Legend: Range of values/number of patients

	<u>Marshall</u>	<u>Leyburn</u>	<u>Caughey</u>
Serum:			
Na .....	139-152/11	--	normal
K .....	4.3-6.2/10	4-4.5/5	normal
Cl .....	96-109/11	--	normal
Ca .....	9.0-11.5/11	--	--
Inorganic phosphate .	2.1-4.1/8	--	--

	<u>Marshall</u>	<u>Drucker</u>	<u>Jacobson</u>	<u>Kuhl</u>
Alkaline phosphatase	3-11/10	--	--	--
Cholesterol	160-325/11	normal/10 greater than 250/4	normal	160-250/2
Total protein ...	6.0-8.0/10	--	9.1/1	--
Albumin .....	4.5-6.4/7	--	3.4/1	--
Globulin .....	0.8-2.6/7	--	5.7/1	--
Serum electro- phoresis ..	normal/3	--	--	--

# LABORATORY DATA FROM LITERATURE

Legend: Range of values/number of patients

	<u>Marshall</u>	<u>Drucker</u>	<u>Becker</u>	<u>Jacobson</u>	<u>Kuhl</u>
I-131			17%/1		
uptake ..	--	15-38/9	normal/1	--	18-52.2%
BMR .....	-50 to +8/6	-17 to +13/15	-13 to -28/3	--	-19 to +29
PBI .....	--	normal/3	normal/3	normal/1	4.3-5.6
Thyroxine turnover .	--	--	--	--	normal
Pool measure-ments .....	--	--	--	--	normal
Circulating thyroid antibodies	--	--	--	--	none

	<u>Marshall</u>	<u>Lakin</u>	<u>Clarke</u>	<u>Amer. Pract.</u>	<u>Caughey</u>	<u>Jacobson</u>
HMG (pit.)						
24 hrs. ...	3-9/7	--	--	--	--	--
Urinary FSH .....	--	104u/pos.	normal/2	in-creased/1	in-creased/9	--
ACTH (IV) .	--	--	--	--	--	normal
ICSH .....	--	--	in-creased	--	--	--

## Drucker

Plasma 17-hydroxycorticoids:

<u>No.</u>	<u>Before ACTH</u>	<u>After ACTH</u>
1	normal	high
5	normal	normal
1	normal	low
4	high	normal
1	high	high
5	no data	no data
range	4-23	35-55

# LABORATORY DATA FROM LITERATURE

Legend: Range of values/number of patients

	<u>Marshall</u>	<u>Becker</u>
Urinary estrogens		normal/2
OE-1 .....	2.9-5.3/7	--
OE-2 .....	0.0-3.8/6	--
OE-3 .....	4.3-18 /7	--
Pregnanediol .....	0.4-2.1/7	--

	<u>Marshall</u>	<u>Drucker</u>
Total 17-hydroxy-corticosteroids .....	5.0-19.6/2	3-9/3 under 3/1
17-oxysteroids .....	4.3-13.2/6	--
Kepler test .....	normal/9	--

Urinary 17-ketosteroids:	<u>Author</u>	<u>Results</u>
	Drucker.....	5-20/3 under 5/8
	Benda .....	decreased/5
	Clarke .....	decreased/2
	Holland .....	slightly decreased/6
	Kuhl .....	decreased
	Caughey .....	decreased/9

Urinary 17-ketogenic steroids:	
	Drucker .....
	under 5/11 5-20/9

## Urinary gonadotropins:

Urinary androgens:	Becker .....	normal/2
Serum aldolase:	Clarke .....	increased
Muscle aldolase:	Pachomov .....	increased/6
Serum aldolase:	Pachomov .....	decreased/6
Urinary excretion:	Kuhl .....	1.7-2.9u/ml./3
amino acids	Carver	
tyrosine		decreased
Creatine, urinary, 24 hrs.	Kuhl .....	58-151 mg./4
Urinary creatinine, 24 hrs.		0.92-1.1 gm.
Lactic dehydrogenase	Kuhl .....	90-117/3
Serum transaminase	Kuhl .....	10-16/3
Sedimentation rate	Jacobson .....	114mm/hr.
Sex chromatin .....	Kuhl .....	4 negatives/4 phenotypic males

# LABORATORY DATA FROM LITERATURE

Legend: Range of values/number of patients

Glucose tolerance curves:

<u>Author</u>	<u>Flat</u>	<u>Normal</u>	<u>Reactive hypoglycemia</u>	<u>Diabetic</u>	<u>Abnormal</u>
Marshall ....	2	6	1	--	--
Becker .....	--	2	--	1	--
Lakin .....	--	--	--	1	--
Phemister ....	--	1	--	--	--
Simon .....	--	--	--	11	--
Stanbury ....	--	--	--	1	--
Ravin .....	--	7	--	--	--
Pachomov ....	1	1	--	--	4
Martin .....	1	--	--	--	--
Miller .....	--	1	--	--	--

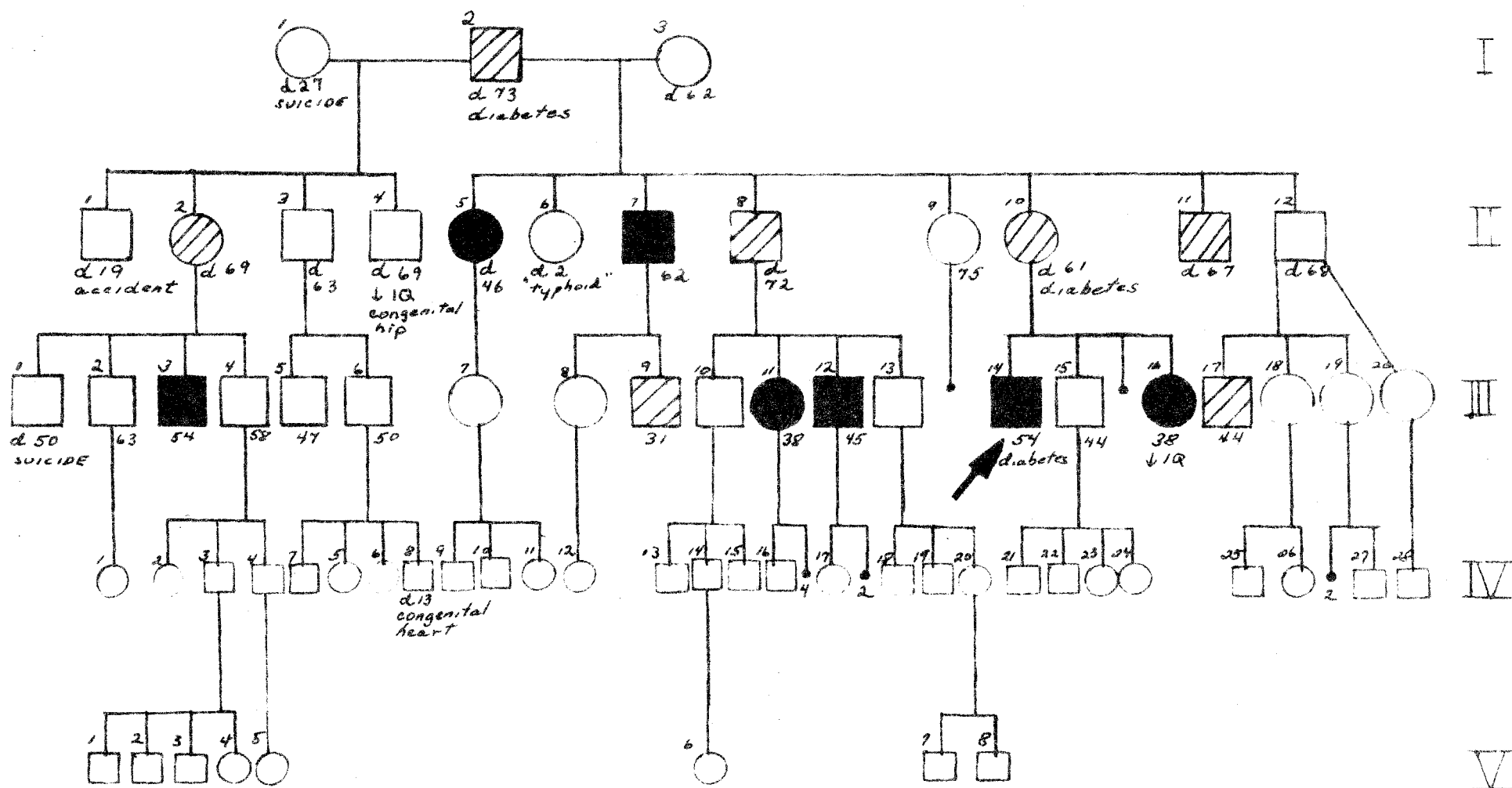
Fasting blood sugars:

## Author

Jacobson ..... 67  
79  
82  
86  
95  
254  
256/total of 7 patients

CAVEAT: It should be noted that the elevated total protein, albumin of 3.4, globulin of 5.7 and sedimentation rate of 114 mm./hr. cited by Jacobson were all obtained on the same patient.

It should also be noted that Becker reported one patient with a PBI of 2.3 mg. as well as the three patients with normal PBI's cited.



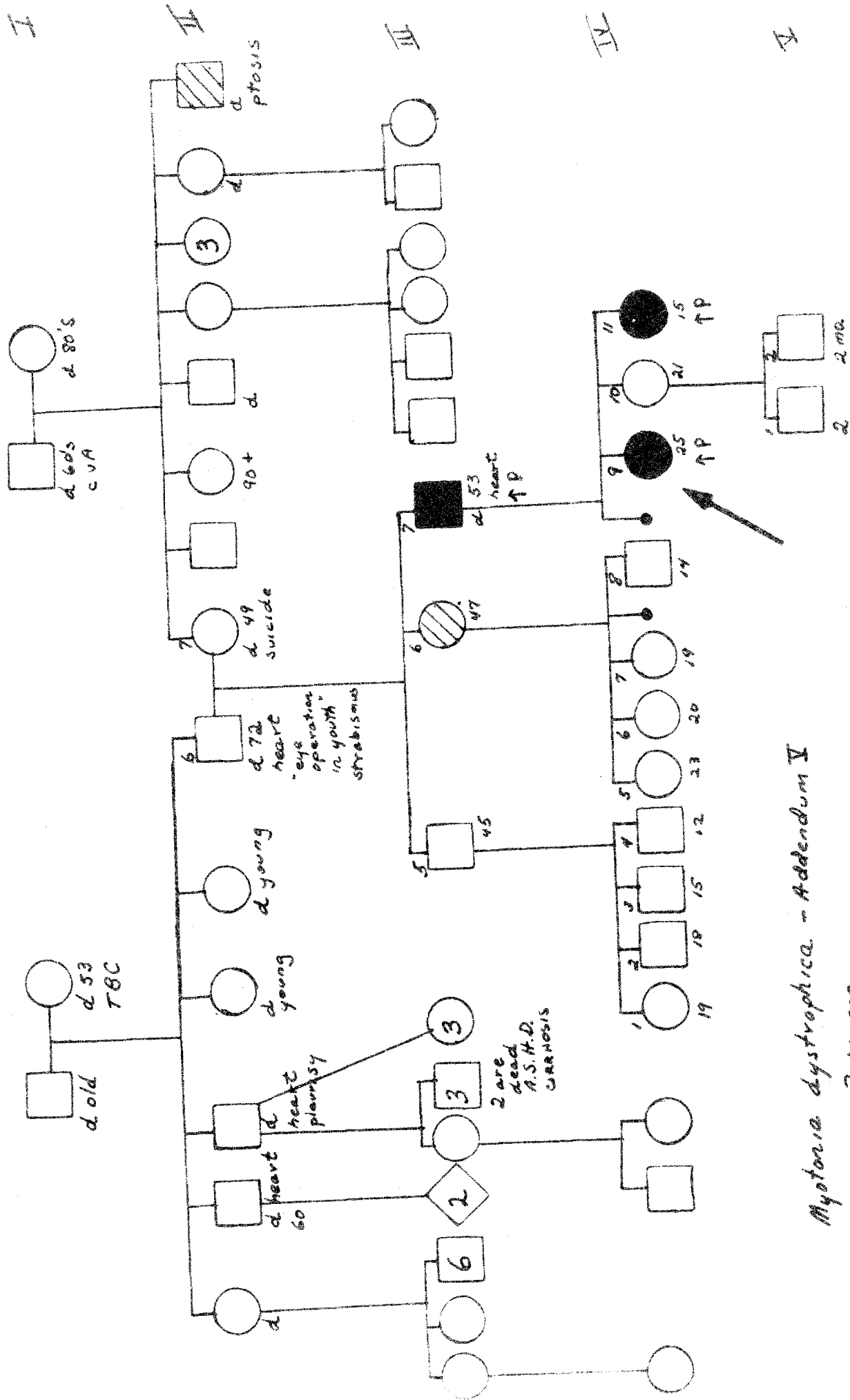
# MYOTONIA DYSTROPHICA

## S Family Pedigree

Addendum IV

- |     |                               |     |                     |
|-----|-------------------------------|-----|---------------------|
| □ ○ | normal                        | 9   | reference number    |
| ▨ ▩ | probable myotonia dystrophica | 75  | age                 |
| ■ ● | proven myotonia dystrophica   | ↓ 2 | number of abortions |
| ↑ P | high arched palate            | 6   | number of siblings  |

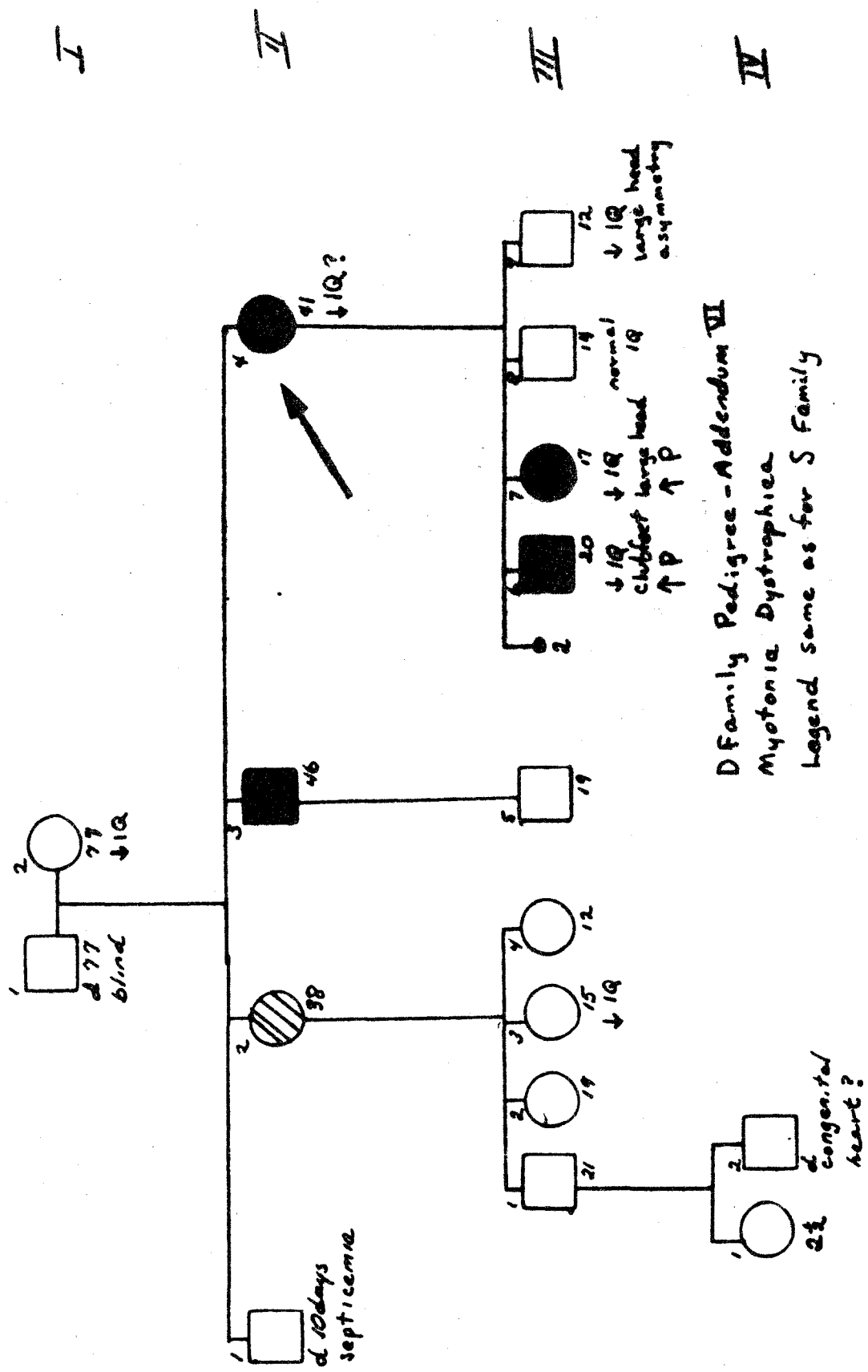




*Myotonia dystrophica - Addendum V*

K Family Pedigree

Legend same as S Family Pedigree



D Family Pedigree - Addendum VI  
 Myotonia Dystrophica  
 Legend same as for S Family

### Acknowledgments

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Rose Greene

February 1, 1964